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ORIGINAL ARTICLE

Effects of sodium–glucose cotransporter 2 inhibitors on non-alcoholic fatty liver disease in patients with type 2 diabetes: A meta-analysis of randomized controlled trials

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Keywords
Non-alcoholic fatty liver disease, Sodium–glucose cotransporter 2 inhibitors, Type 2 diabetes mellitus

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ABSTRACT

Aims/Introduction: Non-alcoholic fatty liver disease (NAFLD) is increasingly common in patients with type 2 diabetes mellitus. Currently, some studies have found that sodium–glucose cotransporter 2 (SGLT2) inhibitors, a new hypoglycemic drug, can improve non-alcoholic fatty liver in addition to its hypoglycemic effect. Thus, we undertook a meta-analysis of randomized controlled trials to evaluate the efficacy of SGLT2 inhibitors on the treatment of NAFLD.

Materials and Methods: PubMed, Embase and the Cochrane Library were searched for randomized controlled trials of SGLT2 inhibitors in patients with NAFLD and type 2 diabetes mellitus up to 1 October 2019. Differences were expressed as weight mean difference (WMD) with 95% confidence interval (CI) for continuous outcomes. The I^2 statistic was applied to evaluate the heterogeneity of studies.

Results: A total of six trials including 309 patients were selected into our meta-analysis. SGLT2 inhibitors could reduce alanine aminotransferase (WMD −11.05 IU/L, 95% CI −19.85, −2.25, $P = 0.01$) and magnetic resonance imaging proton density fat fraction (WMD −2.07%, 95% CI −3.86, −0.28, $P = 0.02$). However, SGLT2 inhibitors did not reduce aspartate aminotransferase (WMD −1.11 IU/L, 95% CI −2.39, 0.17, $P = 0.09$). In addition, secondary outcomes, such as bodyweight and visceral fat area, were also reduced (WMD −1.62 kg, 95% CI −2.02, −1.23, $P < 0.00001$; WMD −19.98 cm^2, 95% CI −27.18, −12.79, $P < 0.00001$, respectively).

Conclusions: SGLT2 inhibitors can significantly decrease alanine aminotransferase and liver fat, accompanied with weight loss, which might have a positive effect on fatty liver in patients with type 2 diabetes mellitus. The limitation is that the sample size of the studies was small. Therefore, more large randomized controlled trials specified on NAFLD are required to evaluate these results.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has been the cause of great public focus worldwide, and is estimated to affect 75% of patients with type 2 diabetes mellitus[1]. According to some studies, up to 30% of patients with NAFLD progress to non-alcoholic steatohepatitis (NASH)[2], and further to liver cirrhosis and hepatocellular carcinoma[3]. Some studies have confirmed that there is a clear and close association between type 2 diabetes mellitus and NAFLD or NASH[4]. Furthermore, the prevalence of NAFLD often accompanies various complications, such as cardiovascular adverse events, in patients with type 2 diabetes mellitus[5], which is detrimental to the prognosis of those patients. Therefore, effective therapy for NAFLD is important for patients with type 2 diabetes mellitus[6]. Nowadays, although we have evidence that pioglitazone, an insulin sensitizer, can improve the function of the liver when it plays a hypoglycemic

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effect, it also has side-effects, such as the increase of subcutaneous fat tissue and bodyweight gain with edema[7].

Sodium–glucose cotransporter 2 (SGLT2) inhibitor is a novel and potent oral hypoglycemic agent used to treat type 2 diabetes mellitus, which can increase urinary glucose excretion, thereby lowering the blood glucose level and bodyweight[8,9]. Some previous studies showed that the effect on weight loss of SGLT2 inhibitors was useful for the alleviation of NAFLD[10,11]. Komiya *et al.*[12] also found SGLT2 inhibitors can significantly reduce bodyweight in NAFLD patients. In addition, more recently, a multi-institutional cohort study[13] suggested that the administration of SGLT2 inhibitors to patients with type 2 diabetes mellitus could improve serum alanine aminotransferase (ALT) levels in clinical practice, particularly for patients with especially high ALT levels. However, there are no specific statistics on the degree of reduction of ALT by SGLT2 inhibitors. Therefore, we carried out a meta-analysis on the effects of several common SGLT2 inhibitors on ALT, liver fat and bodyweight.

METHODS

Search strategy and study selection

We searched PubMed, Embase and the Cochrane Library for relevant articles up to 1 October 2019, with no language restriction. Search terms were MeSH terms and entry terms. For example, for the PubMed database, we searched ("Sodium-Glucose Transporter 2 Inhibitors" [MeSH] OR SGLT2 Inhibitors OR SGLT-2 Inhibitors OR SGLT 2 Inhibitors OR Gliflozins OR Dapagliflozin OR Empagliflozin OR Ipragliflozin OR Ertugliflozin OR Canagliflozin OR Luseogliflozin OR Sotagliflozin) AND ("Nonalcoholic Fatty Liver Disease" [MeSH] OR NAFLD OR Fatty Liver OR Nonalcoholic Steatohepatitis OR Nonalcoholic Steatohepatitides OR NASH). The eligible searches were limited to randomized controlled trials (RCTs). Two reviewers (BD Xing, BZ Dong) independently screened the titles and abstracts of all records, and full texts of potentially eligible studies. Any disagreements were resolved by consensus with a third reviewer (WS Lv). The following inclusive selection criteria were applied. First, populations were patients (aged 20–75 years) with type 2 diabetes mellitus and NAFLD. The glycated hemoglobin (HbA1c) was of 6.0–12.0%. The inclusion criteria for NAFLD were as follows: (i) fatty liver based on imaging examination (ultrasonography or computed tomography); (ii) alcohol intake not exceeding 140 g/week in women and 210 g/week in men; and (iii) exclusion of other causes of liver disease (e.g., viral, autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis and Wilson's disease). Second, the treatment intervention was SGLT2 inhibitors (regardless of which type). Third, the primary outcome was the change of liver enzyme (ALT and aspartate aminotransferase [AST]) and magnetic resonance imaging proton density fat fraction (MRI-PDFF) from baseline. The secondary outcomes were the change of visceral fat area (VFA), bodyweight and HbA1c from baseline. Fourth, the study design was RCT. We excluded case reports, animal experiments, conference abstracts, reviews, subgroup analysis and editorials.

Data extraction and quality assessment

Two independent reviewers (YH Zhao and BZ Dong) extracted the following information from the eligible articles: study characteristics (first author, year of publication, sample size, intervention [type and dose of SGLT2 inhibitor], the medicine of the comparison group, follow-up time), and patients' baseline (age, type 2 diabetes mellitus duration, HbA1c, body mass index) and clinical outcomes (ALT, AST, MRI-PDFF, VFA, bodyweight and HbA1c). At present, MRI-PDFF, based on MRI, is a most accurate indicator to measure liver fat. VFA was measured through abdominal computed tomography.

The quality of RCTs was assessed by the Cochrane risk-of-bias tool, including: (i) random sequence generation (selection bias); (ii) allocation concealment (selection bias); (iii) blinding of participants and personnel (performance bias); (iv) blinding of outcome data (detection bias); (v) incomplete outcome data (attrition bias); (vi) selective reporting (reporting bias); and (vii) other bias: some bias has a great relationship with outcome, but not in the aforementioned items. The judgment for each entry involves answering a question, with "yes" indicating low risk of bias, "no" indicating high risk of bias and unclear indicating a lack of information or uncertainty about the possibility of bias. The quality evaluation was carried out and checked independently by two researchers (BD Xing and YH Zhao). If there is any disagreement, we negotiated with the third researcher (Y Zhou).

Ethical approval

This study complied with the Declaration of Helsinki. Given the study was a meta-analysis, no prior ethical approval was required.

Statistical analysis

Differences were expressed as weight mean difference (WMD) with 95% confidence interval (CI) for continuous outcomes. The I^2 statistic was applied to evaluate the heterogeneity of studies. Studies with an I^2 statistic of 25–50% were considered to have low heterogeneity, those with an I^2 of 50–75% were considered to have moderate heterogeneity and those with an I^2 of >75% were considered to have high heterogeneity. A random effects model was applied regardless of heterogeneity. According to the characteristics of the studies, we further carried out subgroup analyses or sensitivity analyses to explain the reason for heterogeneity as soon as possible. All statistical analyses were carried out with Review Manager version 5.3 (The Cochrane Collaboration, The Nodic Cochrane Center, Copenhagen, Denmark).

RESULTS

Selection results

A total of 408 articles were selected by preliminary search, with 118 articles being duplications. A total of 244 records were eliminated based on the titles and abstracts. Following the full text of

the remaining 46 articles, seven articles were excluded because they were not RCTs, five articles were removed because they were conference abstracts, 21 articles had uncompleted outcomes and six articles were duplications with the same samples. The remaining seven articles met out inclusion criteria. However, one study had too many participants (>1,000) compared with the other six articles, which might affect the final results, so we excluded it. Finally, six studies including 309 participants were eligible for the meta-analysis. The selection process is shown in Figure 1.

Basic characteristics and quality assessment

The characteristics of the included six studies[14-19] are shown in Table 1. In all the studies, the interventions of the experiment groups were dapagliflozin (two studies), empagliflozin (one study), luseogliflozin (one study) and ipragliflozin (two studies), respectively. In addition, in terms of the control group, one study used metformin, one study used pioglitazone, three studies used standard hypoglycemic treatment (according to local guidelines) and one study used a placebo in the background of basic hypoglycemic medicine (mainly metformin and sulfonylureas). Basic hypoglycemic drugs were used throughout the study to control blood glucose. It must be noted that other studies did not involve thiazolidinediones, except for the control group, which was pioglitazone. Glucagon-like peptide-1 receptor agonist, an incretin-based hypoglycemic drug that had a great effect on lowering blood glucose and reducing weight, was not included in any of the studies. We can see the baseline of outcomes in Table 2. In addition, we evaluated the bias of these studies using the Cochrane risk bias assessment tool. Four studies[14,16,17,19] were open-label, with the selective and performance bias being high or unclear. Four studies[14,16,17,9] had no participants drop out, whereas the other two studies[15,18] had participants who were lost to follow up. As for the remaining bias, most of the studies were low risk and the details are shown in Figure S1.

Outcome meta-analysis

ALT and AST

Five studies evaluated the effects of SGLT2 inhibitors on ALT. Overall analysis showed that SGLT2 inhibitors could significantly decrease ALT level (ALT WMD −11.05 IU/L, 95% CI −19.85, −2.25, $P = 0.01$; Figure 2a). However, a heterogeneity test showed that the I^2 of ALT was 73%, suggesting that it had a moderate heterogeneity. We also carried out an analysis for AST level, which showed that SGLT2 inhibitors had no statistical difference on AST reduction (WMD −1.11I U/L, 95% CI −2.39, 0.17; $P = 0.09$; Figure 2b). The I^2 was 0%, showing that the result was stable.

Imaging examination: MRI-PDFF and VFA

Although just two studies used the indicator of MRI-PDFF, both of them showed SGLT2 inhibitors could reduce it (WMD −2.07%, 95% CI −3.86, −0.28, $P = 0.02$). The agents of these two studies were dapagliflozin and empagliflozin. In addition, a heterogeneity test showed $I^2 = 10\%$, suggesting that the result had a very low heterogeneity (Figure 2c). Furthermore, VFA was observed in four studies, the results suggesting that SGLT2 inhibitors could obviously decrease VFA (WMD −19.98 cm^2, 95% CI −27.18, −12.79, $P < 0.0001$; Figure 2d), with a low heterogeneity of results. The I^2 was 37%.

Bodyweight

There were five studies that reported the effect of SGLT2 inhibitors on bodyweight. In contrast with the control group, SGLT2 inhibitors could evidently reduce bodyweight (WMD −1.42 kg, 95% CI −1.64, −1.21, $P < 0.00001$; Figure 2e). Furthermore, a heterogeneity test showed that the result had a low heterogeneity, with $I^2 = 31\%$.

HbA1c

All studies evaluated the indicator of HbA1c. The results showed that SGLT2 inhibitors, compared with other oral antidiabetic drugs (OADs), had no statistical difference on HbA1c reduction (WMD −0.41%, 95% CI −1.16, 0.12, $P = 0.13$; Figure 3). However, the result had high heterogeneity, with $I^2 = 93\%$. Some studies included other effective hypoglycemic agents, which might affect the final outcome, resulting in high heterogeneity as well. Furthermore, in the present meta-analysis, we mainly observed the effect of liver enzyme and liver fat of SGLT2 inhibitors, so we did not carry out further tests for heterogeneity of HbA1c.

Subgroup analyses and sensitivity analyses

Because of its obvious heterogeneity, we made a subgroup analysis for ALT by comparing SGLT2 inhibitor type, control groups, sample size and follow-up time. Based on the differences of the control groups, we carried out further subgroup analysis. We found that SGLT2 inhibitors significantly reduced ALT level compared with standard hypoglycemic treatment (ALT: WMD −17.62 IU/L, 95% CI −29.69, −5.54, $P = 0.004$), whereas the reduction of ALT level was lower, compared with pioglitazone (ALT: WMD −2.5 IU/L, 95% CI −4.29, −0.71, $P = 0.006$). However, compared with metformin, there was no statistical difference of SGLT2 inhibitors on the reduction of ALT (WMD −9.13 IU/L, 95% CI −19.18, 0.92, $P = 0.08$). The difference between groups showed statistically significance ($\chi^2 = 7.36$, $P = 0.03$, $I^2 = 72.8\%$; Figure 4). In addition, stratified by SGLT2 inhibitor type, sample size and follow-up time, we found no statistically significant difference between groups, which were $P = 0.96$, 0.67 and 0.14, respectively (Figures S2–S4).

We also carried out a sensitivity analysis to test for heterogeneity. By deleting the literature one by one, we found that Ito's study might be the source of heterogeneity. After deleting this article, heterogeneity changed from 73 to 37%, and the *P*-value decreased significantly (from 0.01 to 0.001), which might be related to the control group taking pioglitazone. Other outcomes, such as AST, VFA and bodyweight, showed low heterogeneity, so we did not carry out further tests.

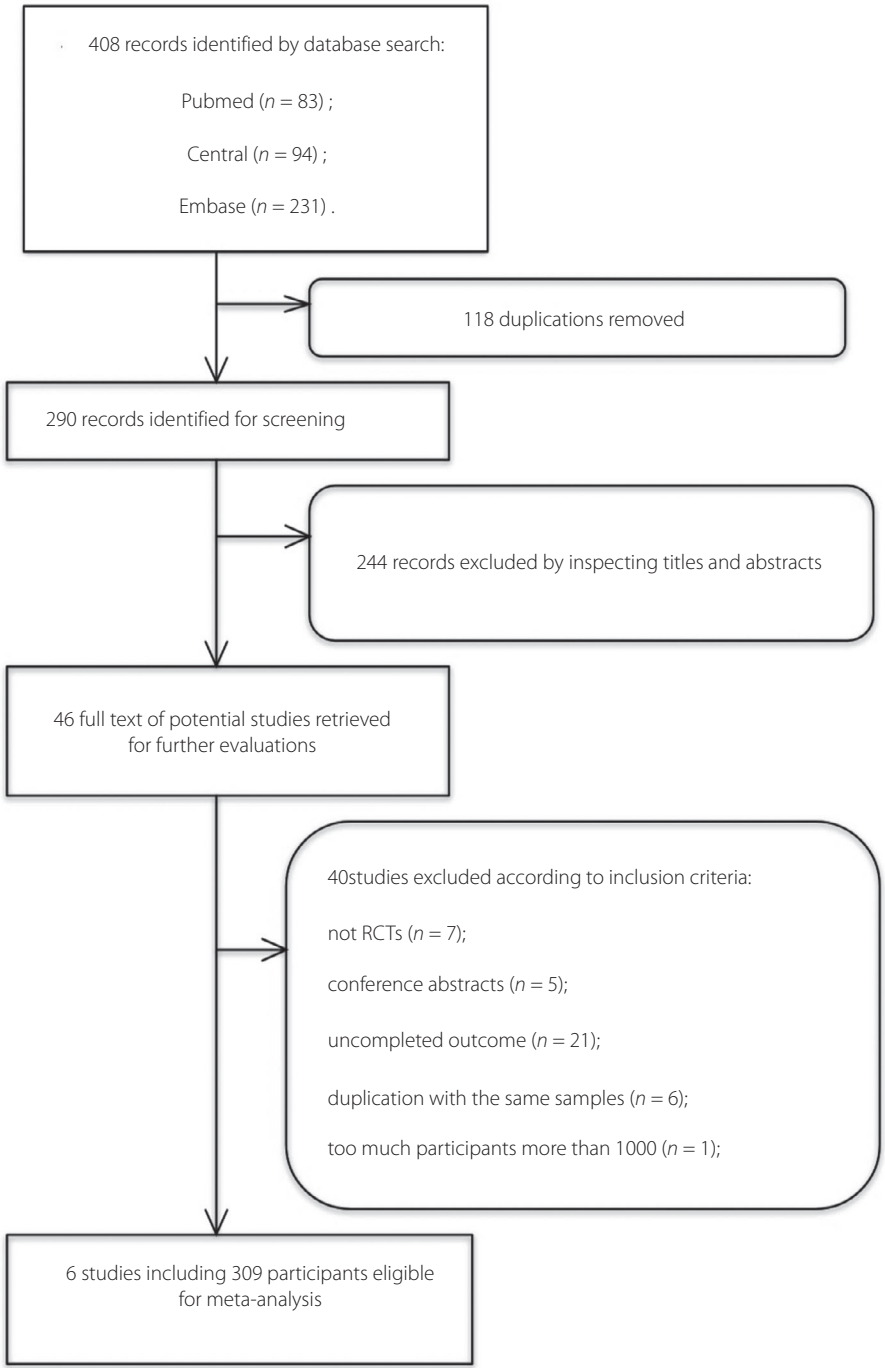


Figure 1 | Flow chart of literature selection. RCTs, randomized controlled trials.

Publication bias

As the number of studies we included was <10, we did not carry out a test of publication bias.

DISCUSSION

The main aim of the present meta-analysis was to evaluate the effect of SGLT2 inhibitors on NAFLD by the change of liver enzyme and liver fat volume. In this meta-analysis, we found that compared with other OADs, SGLT2 inhibitors can significantly decrease ALT (−11.05 IU/L). Although pioglitazone has been shown to have a great effect on the improvement of liver function[6], SGLT2 inhibitors resulted in an additional ALT reduction of 2.5 IU compared with pioglitazone in that study. SGLT2 inhibitors can also reduce AST (−1.11 IU/L); however, the reduction is slight and shows no statistical difference, considering the reason might be that AST is not a very specific indicator of fat liver

Table 1 | Basic characteristic of included six studies

Author	Year published	Sample (F)	Age (years)	Intervention		Duration (years)	Follow-up time
				Experiment group	Control group		
Ito D	2017	66 (34)	58.2 (10.9)	Ipragliflozin: 50 mg	Pioglitazone: 15–30 mg	9.1 (5.8)	24 weeks
Aso Y	2019	57 (23)	55.0 (8.6)	Standard hypoglycemic treatment + dapagliflozin 5 mg	Standard hypoglycemic treatment	NR	24 weeks
Bando Y	2017	62 (22)	NR	Continued hypoglycemic treatment + ipragliflozin 50 mg	Continued hypoglycemic treatment	9.6 (4.5)	12 weeks
Kuchay MS	2018	50 (20)	65.3 (6.23)	Standard hypoglycemic treatment + empagliflozin 10 mg	Standard hypoglycemic treatment	NR	20 weeks
Eriksson JM	2018	42 (9)	65.3 (6.23)	Dapagliflozin: 10 mg	Placebo	6.6 (5.1)	12 weeks
Shibuya	2017	32 (14)	56.5 (11.68)	Luseogliflozin: 5 mg	Metformin: 1,500 mg	9.6 (10)	6 months

Data are the mean (standard deviation) in age and duration. F, female; NR, not reported.

Table 2 | Baseline characteristic of participants in the six included studies

Author	BMI		Weight (kg)		HbA1c (%)	
	Experiment group	Control group	Experiment group	Control group	Experiment group	Control group
Ito D	30.7 (5.0)	29.9 (6.2)	79.6 (17.9)	76.7 (15.2)	8.5 (1.5)	8.3 (1.4)
Aso Y	27.6 (4.7)	28.3 (3.5)	73.9 (16.1)	76.4 (13.9)	8.37 (1.48)	7.7 (1.24)
Bando Y	27.8 (3.9)	27.3 (3.1)	NR	NR	8.1 (1.0)	8.2 (1.1)
Kuchay MS	30.0 (3.8)	29.4 (3.1)	80.8 (13.0)	81.1 (13.0)	9.0 (1.0)	9.1 (1.4)
Eriksson JM	30.5 (2.8)	30.3 (3.1)	90.2 (8.7)	93.0 (12.2)	7.38 (0.56)	7.44 (0.80)
Shibuya	27.6 (2.03)	28.03 (5.77)	76.27 (18.2)	75.4 (19.1)	7.3 (0.65)	7.6 (0.57)

Author	ALT (U/L)		AST (U/L)		VFA (cm^2)		MRI-PDFF (%)	
	Experiment group	Control group	Experiment group	Control group	Experiment group	Control group	Experiment group	Control group
Ito D	57.4 (27.3)	53.1 (26.6)	39.7 (16.7)	43.3 (20.5)	154.5 (52.4)	158.7 (68.2)	NR	NR
Aso Y	40.2 (30.6)	34.7 (17.3)	32.8 (22.7)	29.8 (12.8)	108.7 (42.9)	125.7 (38.2)	NR	NR
Bando Y	49 (36)	41 (35)	35 (19)	30 (17)	186 (83)	181 (89)	NR	NR
Kuchay MS	64.3 (20.2)	65.3 (40.3)	44.6 (23.5)	45.3 (24.3)	NR	NR	NR	NR
Eriksson JM	NR	NR	NR	NR	NR	NR	17.3 (9.1)	15.1 (6.5)
Shibuya	50.17 (31.70)	39.3 (26.82)	NR	NR	146.53 (59.42)	149.23 (59.5)	16.2 (7.0)	16.4 (7.3)

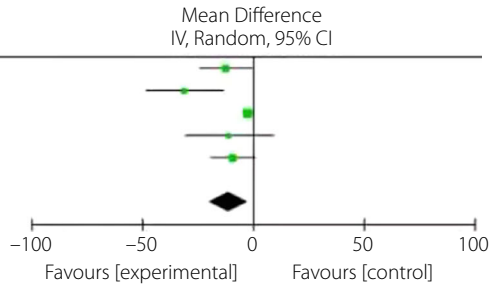
Data are the mean (standard deviation). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; MRI-PDFF, magnetic resonance imaging proton density fat fraction; NR, not reported; VFAs, visceral fat areas.

and is susceptible to other factors. The above results are consistent with the results of a large study we excluded (because of too many participants)[20]. The study included the EMPA-REG OUTCOME® trial (n = 7,020), pooled data from four 24-week placebo-controlled trials (n = 2,477) and a trial of empagliflozin versus glimepiride over a period of 104 weeks (n = 1,545), showing highly consistent results that empagliflozin could reduce aminotransferases in individuals with type 2 diabetes mellitus, with the reductions of ALT being more than AST. Furthermore, it is worth mentioning that although there were just two articles, both of them showed that SGLT2 inhibitors can decrease liver fat content by 2.07%, as measured by MRI-PDFF. MRI-PDFF is a quantitative MRI-based biomarker that can accurately estimate liver fat content and evaluate the treatment response in NASH clinical trials[21]. Therefore, the reduction of MRI-PDFF illustrates that SGLT2 inhibitors have a beneficial effect on reducing liver fat, which shows a guiding significance for the application of SGLT2 inhibitors on NAFLD in the future. In addition, in the analysis, we found that SGLT2 inhibitors show great superiority to other OADs on the reduction of VFA (−19.98 cm^2) and bodyweight (−1.62 kg), which can also demonstrate that SGLT2 inhibitors are helpful to improve NAFLD. However, in our meta-analysis, SGLT2 inhibitors did not show a greater effect on the reduction of HbA1c than other OADs. We suspect it might have a relationship to study itself, because background glucose-lowering therapy is different in some studies. In addition, it might indicate that the decrease of ALT and MRI-PDFF have nothing to do with whether HbA1c reduces or not. In other words, the improvement of NAFLD by SGLT2 inhibitors might be independent of the hypoglycemic effect.

(a)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Aso Y2019	−11.74	26.98	33	0.7	18.27	24	20.2%	−12.44 [−24.19, −0.69]
Bando Y2017	−18	25	37	13	35	20	14.2%	−31.00 [−48.33, −13.67]
Ito D2017	−20	3.4	32	−17.5	4	34	31.2%	−2.50 [−4.29, −0.71]
Kuchay MS2018	−14.6	23.51	22	−3.7	39.38	20	12.1%	−10.90 [−30.76, 8.96]
Shibuya2017	−9.3	17.07	16	−0.17	11.38	16	22.4%	−9.13 [−19.18, 0.92]
Total (95% CI)			140			114	100.0%	−11.05 [−19.85, −2.25]

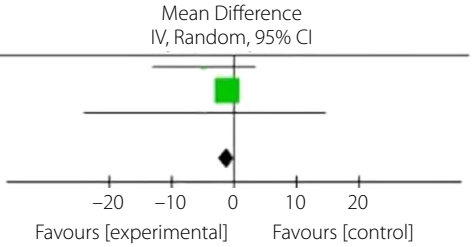
Heterogeneity: Tau^2 = 63.79; Chi^2 = 14.76, df = 4 (P = 0.005); I^2 = 73%
Test for overall effect: Z = 2.46 (P = 0.01)



(b)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Aso Y2019	−7.24	19.67	33	−2.4	11.54	24	2.5%	−4.84 [−12.99, 3.31]
Ito D2017	−12.6	2.1	32	−11.6	3.2	34	97.1%	−1.00 [−2.30, 0.30]
Kuchay MS2018	−8.4	20.54	22	−3.7	39.38	20	0.4%	−4.70 [−23.98, 14.58]
Total (95% CI)			87			78	100.0%	−1.11 [−2.39, 0.17]

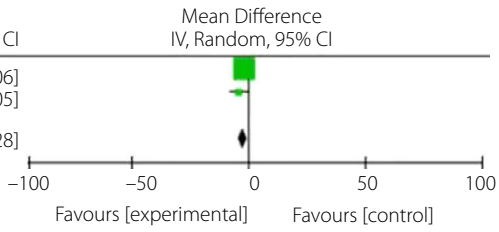
Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.97, df = 2 (P = 0.62); I^2 = 0%
Test for overall effect: Z = 1.70 (P = 0.09)



(c)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Eriksson JM2018	−2.23	3.3	19	−0.59	1.86	19	81.6%	−1.64 [−3.34, 0.06]
Kuchay MS2018	−8.4	20.54	22	−3.7	39.38	20	0.4%	−4.00 [−8.05, 0.05]
Total (95% CI)			41			39	100.0%	−2.07 [−3.86, −0.28]

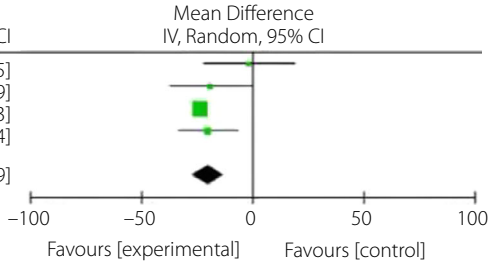
Heterogeneity: Tau^2 = 0.27; Chi^2 = 1.11, df = 1 (P = 0.29); I^2 = 10%
Test for overall effect: Z = 2.27 (P = 0.02)



(d)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Aso Y2019	−7.3	41.17	33	−5.7	36.79	24	10.4%	−1.60 [−21.95, 18.75]
Bando Y2017	1.4	18.9	37	20.4	39.4	20	12.3%	−19.00 [−37.31, −0.69]
Ito D2017	−26.1	4.9	32	−2.6	4.9	34	57.5%	−23.50 [−25.87, −21.13]
Shibuya2017	−15.87	21.86	16	4.17	16.09	16	19.8%	−20.04 [−33.34, −6.74]
Total (95% CI)			118			94	100.0%	−19.98 [−27.18, −12.79]

Heterogeneity: Tau^2 = 22.01; Chi^2 = 4.79, df = 3 (P = 0.19); I^2 = 73%
Test for overall effect: Z = 5.44 (P < 0.00001)



(e)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Aso Y2019	−3.9	15.5	33	−0.6	13.33	24	0.3%	−3.30 [−10.81, 4.21]
Bando Y2017	−1.51	1.28	40	0.45	0.77	22	31.6%	−1.96 [−2.47, −1.45]
Eriksson JM2018	−2.44	2.14	19	−0.27	1.79	19	8.6%	−2.17 [−3.42, −0.92]
Ito D2017	−2.3	0.5	32	−0.9	0.4	34	55.9%	−1.40 [−1.62, −1.18]
Kuchay MS2018	−1.3	3.7	22	−0.6	3	20	3.6%	−0.70 [−2.73, 1.33]
Total (95% CI)			146			119	100.0%	−1.62 [−2.02, −1.23]

Heterogeneity: Tau^2 = 0.06; Chi^2 = 5.83, df = 4 (P = 0.21); I^2 = 31%
Test for overall effect: Z = 8.09 (P < 0.00001)

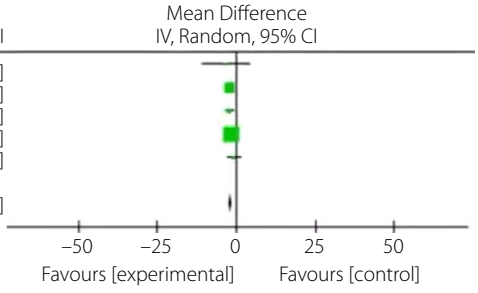


Figure 2 | (a) Forest plots showing alanine aminotransferase level comparisons between sodium–glucose cotransporter 2 (SGLT2) inhibitors and the control group. (b) Forest plots showing aspartate aminotransferase level comparisons between SGLT2 inhibitors and the control group. (c) Forest plots showing magnetic resonance imaging proton density fat fraction comparisons between SGLT2 inhibitors and the control group. (d) Forest plots showing visceral fat areas comparisons between SGLT2 inhibitors and the control group. (e) Forest plots showing bodyweight comparisons between SGLT2 inhibitors and the control group. CI, confidence interval; SD, standard deviation.

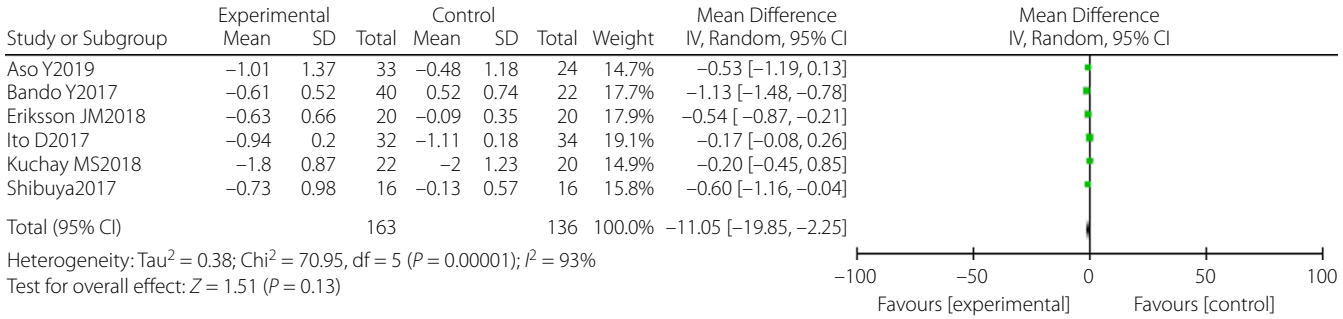


Figure 3 | Forest plots depicting glycated hemoglobin comparisons between sodium–glucose cotransporter 2 inhibitors and the control group. CI, confidence interval; SD, standard deviation.

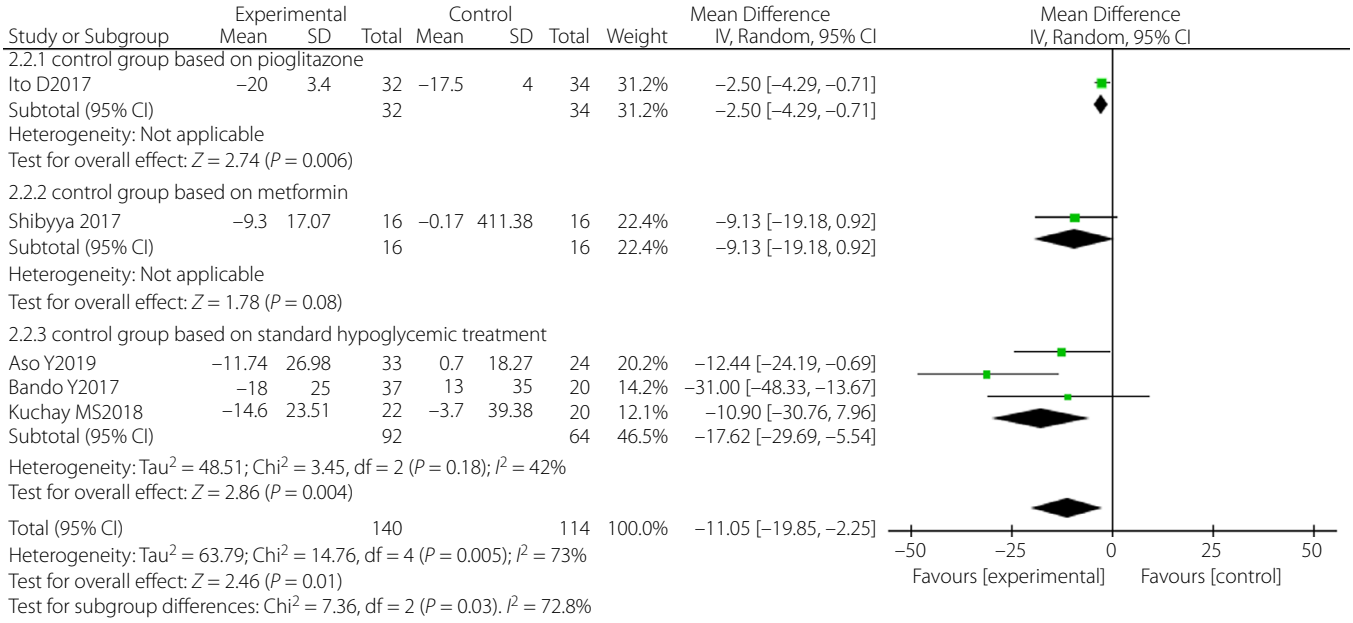


Figure 4 | Forest plots depicting alanine aminotransferase level comparisons between sodium–glucose cotransporter 2inhibitors and the control group based on the control. CI, confidence interval; SD, standard deviation.

The possible mechanisms of SGLT2 inhibitors to improve NAFLD are as follows. First, decreasing inflammatory markers and oxidation stress. The increase in fatty acid oxidation instead of carbohydrate oxidation could also play a role in the reduction of hepatic fat accumulation and might also suppress hepatic inflammation[22]. SGLT2 inhibitors have shown that they can reduce inflammatory markers, accelerate lipolysis, reduce glucose oxidation, decrease oxidative stress and increase oxidation of free fatty acids, which are quite important in the improvement of NAFLD[23]. In addition, a recent study showed that canagliflozin has a beneficial effect on NAFLD by upregulating zinc-α2-glycoprotein levels, reducing hepatic inflammatory cytokines and lowering oxidative stress in the liver[24]. Therefore, the reduction of liver inflammatory factors and oxidation by SGLT2 inhibitors might be one mechanism to improve NAFLD. Second, weight loss. SGLT2 inhibitors can cause energy loss through increasing urine glucose excretion, thereby reducing visceral adiposity and bodyweight [25]. This energy loss might promote β-oxidation in the liver and visceral adiposity, as well as induce liver fat metabolism. In NAFLD therapy, bodyweight loss through lifestyle intervention is considered a basic and effective therapy[26], suggesting that weight loss accompanying visceral fat is beneficial for improving NAFLD. Third, improving glucose control. Carbohydrate response element-binding protein is a transcription factor in the liver that can cause excessive carbohydrate conversion to fat for long-term storage. SGLT2 inhibitors can promote glycosuria, which decrease blood glucose level. Glycemic control has a significant role in down-regulate carbohydrate response element-binding protein, which is helpful to reduce liver fat[27]. Fourth, improving insulin resistance. The main pathological condition in NAFLD patients is insulin resistance. Several studies showed that improving insulin resistance and sensitivity reduces the extent of fatty liver disease, and might prevent the second-step in hepatocyte injury caused by

oxidative stress[28,29]. SGLT2 inhibitors were found to have anti-steatotic and anti-inflammatory effects in a mouse model of NASH and diabetes[30], which can improve insulin resistance. Fifth, glucagon effect. A previous study showed that glucagon can significantly decrease levels of serum triglycerides, cholesterol and very low-density lipoprotein cholesterol[31], as well as reduce lipogenesis, increase liver gluconeogenesis and β- oxidation of liver fat[32], which ultimately improve NAFLD. A recent study[33] suggested that SGLT2 inhibitors might promote glucagon secretion by regulating SGLT1 in islet α-cells; however, the specific mechanism is not clear. Sixth, ketone body metabolism. Ketogenesis can dispose of much of the fat entering the liver, and dysfunction in this pathway could potentially contribute to NAFLD pathogenesis. Cotter's findings[34] suggest that ketogenesis might prevent fatty liver injury and hepatic steatosis through regulating hepatic acetyl coenzyme A metabolism, glucose metabolism and tricarboxylic acid cycle function. The latest research[35] shows that SGLT2 inhibitors could increase ketone body metabolism by upregulating ketogenic enzymes and transporters in the liver, which might be a significant part of the improvement of NAFLD.

The highlight of the present meta-analysis is that it confirms that SGLT2 can improve NAFLD by the reduction of ALT and liver fat, which opens a new door for the treatment of NAFLD in the future, although there were some certain limitations. First, the sample size of included studies was small, which might cause inhomogeneity of results. Therefore, a greater number of large RCTs are required to further validate the present results. Second, the follow-up time was too short to see the long-term effects of SGLT2 inhibitors. Future studies will need to extend the follow-up period to determine whether SGLT2 continues to improve NAFLD. Finally, the present study mainly evaluated whether SGLT2i could improve NAFLD from liver injury markers and liver fat changes, and did not prove whether it was effective in liver histological changes. Further studies are required to evaluate the impact of SGLT2 inhibitors from liver histology.

In summary, SGLT2 inhibitors can significantly reduce liver injury markers and liver fat, along with the effect of weight loss. Furthermore, the effect on improving NAFLD of SGLT2 inhibitors might be independent of hypoglycemic effect. In brief, compared with other OADs, SGLT2 inhibitors have a beneficial effect on improving fatty liver, and are expected to become a new option for the treatment of type 2 diabetes mellitus with NAFLD.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Quality evaluation chart of included studies.

Figure S2 | Forest plots depicting ALT level comparisons between SGLT2 inhibitors and control group based on the types of SGLT2 inhibitors.

Figure S3 | The comparison of ALT level between SGLT2 inhibitors and control group based on sample size.

Figure S4 | Forest plots depicting ALT level comparisons between SGLT2 inhibitors and control group based on follow-up time.